(Sec. 307(a), Federal Aviation Act of 1958, as amended, (49 U.S.C. 1348(a)); sec. 6(c), Department of Transportation Act (49 U.S.C. 1655(c)))

Issued in Aurora, Colorado, on February 4, 1975.

M. M. MARTIN,
Director, Rocky Mountain Region.

In § 71.181 (40 FR 441) amend the description of the Livingston, Mont. transition area to read as follows:

LIVINGSTON, MONT.

That airspace extending upward from 700 feet above the surface within 9.5 miles west and 4.5 miles east of the Livingston VORTAC 340° radial extending from the VORTAC to 18.5 miles north of the VORTAC and within 2.5 miles each side of the Livingston 085° radial, extending from a 5-mile radius circle centered on Mission Field Airport, Livingston, Mont. (latitude 45°41'45" N., longitude 110°26'40" W.) to 9 miles east of the VORTAC; that airspace extending upward from 1,200 feet above the surface within 6 miles south and 9.5 miles north of the Livingston VORTAC 085° and 265° radials, extending from 7 miles west to 21 miles east of the VORTAC.

[FR Doc.75-3191 Filed 2-4-75;8:45 am]

Title 15—Commerce and Foreign Trade

CHAPTER IX—NATIONAL OCEANIC AND ATMOSPHERIC ADMINISTRATION, DEPARTMENT OF COMMERCE

PART 924—MONITOR MARINE SANCTUARY

Interim Regulations

JANUARY 31, 1975.

On January 30, 1975, the Secretary of Commerce designated as a marine sanctuary an area of the Atlantic Ocean around and above the submerged wreckage of the Civil War ironclad Monitor pursuant to the authority of section 302 (a) of the Marine Protection, Research and Sanctuaries Act of 1972 (86 Stat. 1052, 1061, hereafter the Act). The sanctuary area (hereafter the Sanctuary) is about 16.10 miles south-southeast of Cape Hatteras (North Carolina) Light.

Section 302(f) of the Act directs the Secretary to issue necessary and reasonable regulations to control any activities permitted within a designated marine sanctuary. This section also provides that no permit, license, or other authorization issued pursuant to any other authority shall be valid unless the Secretary shall certify that the permitted activity is consistent with the purposes of Title III of the Act ("Marine Sanctuaries"); and that it can be carried out within the regulations promulgated under section 302(f).

The authority of the Secretary to administer the provisions of the Act has been delegated to the Administrator, National Oceanic and Atmospheric Administration, U.S. Department of Commerce (hereafter the Administrator, 39 FR 10255, March 19, 1974).

There are published herewith interim regulations relating to activities to be prohibited or permitted in the Sanctuary, and relating to the certification requirement described above. Comments upon these regulations are invited through March 7, 1975. Comments should be addressed to the Administrator, National Oceanic and Atmospheric Administration, U.S. Department of Commerce, Washington, D.C. 20230. Following the close of this 30-day period, any comments received will be reviewed. In the discretion of the Administrator, these interim regulations will be amended so as to reflect any such comments. The Administrator shall then publish final regulations in the FEDERAL REGISTER. As authorized by 5 U.S.C. 553(d)(3), these interim regulations are effective in order to protect the wreckage until final regulations become effective.

Sec.
924.1 Authority
924.2 Description of the Sanctuary
924.3 Activities Prohibited Within the Sanctuary
924.4 Penalties for Commission of Prohibited Acts
924.5 Permitted Activities
924.6 Permit Procedures and Criteria
924.7 Certification Procedures
924.8 Appeals of Administrative Action

§ 924.1 Authority.

The Sanctuary has been designated by the Secretary of Commerce pursuant to the authority of section 302(a) of the Act. The following regulations are issued pursuant to the authorities of sections 302(f), 302(g) and 303 of the Act.

§ 924.2 Description of the Sanctuary.

The Sanctuary consists of a portion of the water column in the Atlantic Ocean one mile in diameter extending from the surface to the seabed and around and above the submerged wreckage of the Monitor. The central point of the Sanctuary is about 16.10 nautical miles south-southeast of the Cape Hatteras (North Carolina) Light at the coordinates of 35°00'23" north latitude and 75°24'32" west longitude.

§ 924.3 Activities Prohibited Within the Sanctuary.

Except as may be permitted by the Administrator, no person subject to the jurisdiction of the United States shall conduct, nor cause to be conducted, any of the following activities in the Sanctuary:

(a) bottom anchoring;

(b) any type of subsurface salvage or recovery operation;

(c) any type of diving, whether by an individual or by a submersible;

(d) lowering below the surface of the water any grappling, suction, conveyor, dredging or wrecking device;

(e) detonation below the surface of the water of any explosive or explosive mechanism;

(f) seabed drilling or coring;

(g) lowering, laying, positioning or raising any type of seabed cable or cable-laying device;

(h) trawling; or

(i) discharging waste material into the water.

§ 924.4 Penalties for Commission of Prohibited Acts.

Section 303 of the Act authorizes the assessment of a civil penalty of not more than $50,000 for each violation of any regulation issued pursuant to Title III of the Act, and further authorizes a proceeding *in-rem* against any vessel used in violation of any such regulation. Details are set out in Subpart (D) of Part 922 of this Chapter (39 FR 23254, 23257, June 27, 1974). Subpart (D) is applicable to any instance of a violation of these regulations.

§ 924.5 Permitted Activities.

Any person or entity may conduct in the Sanctuary any activity listed in § 924.3 of this Part if: (a) such activity is either (1) for the purpose of research related to the Monitor, or (2) is in connection with an air or marine casualty or the avoidance of same; and (b) such person or entity is in possession of a valid permit issued by the Administrator authorizing the conduct of such activity; except that, no permit is required for the conduct of any activity immediately necessary in connection with an air or marine casualty.

§ 924.6 Permit Procedures and Criteria.

(a) Any person or entity who wishes to conduct in the Sanctuary an activity for which a permit is authorized by § 924.5 (hereafter a permitted activity) may apply in writing to the Administrator for a permit to conduct such activity citing this Section as the basis for the application. Such application should be made to the Administrator, National Oceanic and Atmospheric Administration, U.S. Department of Commerce, Washington, D.C. 20230. Upon receipt of such application, the Administrator shall request, and such person or entity shall supply to the Administrator, such information and in such form as the Administrator may require to enable him to act upon the application.

(b) In considering whether to grant a permit for the conduct of a permitted activity for the purpose of research related to the Monitor, the Secretary shall evaluate such matters as (1) the general professional and financial responsibility of the applicant; (2) the appropriateness of the research method(s) envisioned to the purpose(s) of the research; (3) the extent to which the conduct of any permitted activity may diminish the value of the Monitor as a source of historic, cultural, aesthetic and/or maritime information; (4) the end value of the research envisioned; and (5) such other matters as the Administrator deems appropriate.

(c) In considering whether to grant a permit for the conduct of a permitted activity in the Sanctuary in relation to an air or marine casualty, the Administrator shall consider such matters as (1) the fitness of the applicant to do the work envisioned; (2) the necessity of conducting such activity; (3) the appropriateness of any activity envisioned to the purpose of the entry into the Sanctuary; (4) the extent to which the conduct of any such activity may diminish the value of the Monitor as a source of historic, cultural, aesthetic and/or maritime information; and (5) such other matters as the Administrator deems appropriate.

(d) In considering any application submitted pursuant to this section, the Administrator may seek and consider the views of any person or entity, within or outside of the Federal Government, as he deems appropriate; except that, he shall seek and consider the views of the Advisory Council on Historic Preservation.

(e) The Administrator may, in his discretion, grant a permit which has been applied for pursuant to this Section, in whole or in part, and subject to such condition(s) as he deems appropriate, *except that* the Administrator shall attach to any permit granted for research related to the Monitor the condition that any information and/or artifact(s) obtained in the research shall be made available to the public. The Administrator may observe any activity permitted by this section; and/or may require the submission of one or more reports of the status or progress of such activity.

(f) A permit granted pursuant to this section is nontransferable.

(g) The Administrator may amend, suspend or revoke a permit granted pursuant to this Section, in whole or in part, temporarily or indefinitely, if, in his view, the permit holder (hereafter the Holder) has acted in violation of the terms of the permit; or the Administrator may do so for other good cause shown. Any such action shall be in writing to the Holder, and shall set forth the reason(s) for the action taken. Any Holder in relation to whom such action has been taken may appeal the action as provided in § 924.8 of this Part.

§ 924.7 Certification Procedures.

Any Federal agency which, as of the effective date of these regulations, already has permitted, licensed or otherwise authorized any activity in the Sanctuary shall notify the Administrator of this fact in writing. The writing shall include a reasonably detailed description of such activity, the person(s) involved, the beginning and ending dates of such permission, the reason(s) and purposes(s) for same, and a description of the total area affected. The Administrator shall then decide whether the continuation of the permitted activity, in whole or in part, or subject to such condition(s) as he may deem appropriate, is consistent with the purposes of Title III of the Act and can be carried out within these regulations. He shall inform the Federal agency of his decision in these regards, and the reason(s) therefore, in writing. The decision of the Secretary made pursuant to this section shall be final action for the purpose of the Administrative Procedure Act.

§ 924.8 Appeals of Administrative Action.

(a) In any instance in which the Administrator, as regards a permit authorized by, or issued pursuant to, this Part: (1) denies a permit; (2) issues a permit embodying less authority than was requested; (3) conditions a permit in a manner unacceptable to the applicant; or (4) amends, suspends, or revokes a permit for a reason other than the violation of regulations issued under this Part, the applicant or the permit holder, as the case may be (hereafter the Appellant), may appeal the Administrator's action to the Secretary. In order to be considered by the Administrator, such appeal shall be in writing, shall state the action(s) appealed and the reason(s) therefore; and shall be submitted within 30 days of the action(s) by the Administrator to which the appeal is directed. The Appellant may request a hearing on the appeal.

(b) Upon receipt of an appeal authorized by this section, the Secretary may request, and if he does, the Appellant shall provide, such additional information and in such form as the Secretary may request in order to enable him to act upon the appeal. If the Appellant has not requested a hearing, the Secretary shall decide the appeal upon (1) the basis of the criteria set out in §§ 924.6 (b) or 924.6(c) of this part, as appropriate, (2) information relative to the application on file in NOAA, (3) information provided by the Appellant, and (4) such other considerations as he deems appropriate. He shall notify the Appellant of his decision, and the reason(s) therefore, in writing within 30 days of the date of his receipt of the appeal.

(c) If the Appellant has requested a hearing, the Secretary shall grant an informal hearing before a Hearing Officer designated for that purpose by the Secretary after first giving notice of the time, place, and subject matter of the hearing in the FEDERAL REGISTER. Such hearing shall be held no later than 30 days following the Secretary's receipt of the appeal. The Appellant and any interested person may appear personally or by counsel at the hearing, present evidence, cross-examine witnesses, offer argument and file a brief. Within 30 days of the last day of the hearing, the Hearing Officer shall recommend in writing a decision to the Secretary based upon the considerations outlined in paragraph (b) of this section and based upon the record made at the hearing.

(d) The Secretary may adopt the Hearing Officer's recommended decision, in whole or in part, or may reject or modify it. In any event, the Secretary shall notify the Appellant of his decision, and the reason(s) therefore, in writing within 15 days of his receipt of the recommended decisions of the Hearing Officer. The Secretary's action, whether without or after a hearing, as the case may be, shall constitute final action for the purposes of the Administrative Procedure Act.

ROBERT M. WHITE,
Administrator.

[FR Doc.75-3286 Filed 2-4-75;8:45 am]

Title 21—Food and Drugs

CHAPTER I—FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

SUBCHAPTER B—FOOD AND FOOD PRODUCTS

PART 121—FOOD ADDITIVES

Subpart D—Food Additives Permitted in Food for Human Consumption

AMYLOGLUCOSIDASE ENZYME PRODUCT

The Commissioner of Food and Drugs, having evaluated data in a petition (FAP OA2569) filed by Biocon Ltd., Hall Lane, Rookery Bridge, Nr. Sandbach, Cheshire, CW11 9QZ, England (present address: Grenagh, Rathduff, County Cork, Ireland), and other relevant material, concludes that the food additive regulations (21 CFR Part 121) should be amended, as set forth below, to provide for the safe use of an amyloglucosidase enzyme product for degrading gelatinized starch into constituent sugars.

Therefore, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (sec. 409(c)(1), 72 Stat. 1786; 21 U.S.C. 348(c)(1)), and under authority delegated to the Commissioner (21 CFR 2.120), Part 121 is amended by adding a new section to Subpart D as follows:

§ 121.1265 Amyloglucosidase enzyme product.

Amylglucosidase enzyme product, consisting of enzyme derived from *Rhizopus niveus*, and diatomaceous silica as a carrier, may be safely used in food in accordance with the following conditions:

(a) *Rhizopus niveus* is classified as follows: Class, Phycomycetes; order, Mucorales; family, Mucoraceae; genus, *Rhizipus;* species, *niveus*.

(b) The strain of *Rhizopus niveus* is nonpathogenic and nontoxic in man or other animals.

(c) The enzyme is produced by a process which completely removes the organism *Rhizopus niveus* from the amyloglucosidase.

(d) The additive is used or intended for use for degrading gelatinized starch into constituent sugars, in the production of distilled spirits and vinegar.

(e) The additive is used at a level not to exceed 0.1 percent by weight of the gelatinized starch.

Any person who will be adversely affected by the foregoing order may at any time on or before March 7, 1975 file with the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20852, written objections thereto. Objections shall show wherein the person filing will be adversely affected by the order, specify with particularity the provisions of the order deemed objectionable, and state the grounds for the objections. If a hearing is requested, the objections shall state the issues for the hearing, shall be supported by grounds factually and legally sufficient to justify the relief

sought, and shall include a detailed description and analysis of the factual information intended to be presented in support of the objections in the event that a hearing is held. Objections may be accompanied by a memorandum or brief in support thereof. Six copies of all documents shall be filed. Received objections may be seen in the above office during working hours, Monday through Friday.

Effective date: This order shall become effective February 5, 1975.

(Sec. 409(c)(1), 72 Stat. 1786; 21 U.S.C. 348(c)(1))

Dated: January 29, 1975.

SAM D. FINE,
Associate Commissioner for Compliance.

[FR Doc.75-3196 Filed 2-4-75;8:45 am]

SUBCHAPTER D—DRUGS FOR HUMAN USE

PART 310—NEW DRUGS

Diethylstilbestrol as Postcoital Oral Contraceptive; Patient Labeling

In the FEDERAL REGISTER of September 26, 1973 (38 FR 26809) the Commissioner of Food and Drugs proposed to amend § 130.45 (subsequently recodified as § 310.501 and published in the FEDERAL REGISTER of March 29, 1974 (39 FR 11680)) by redesignating the existing text of the entire section as paragraph (a) and by adding a new paragraph (b) establishing requirements for marketing diethylstilbestrol (DES) for use as a postcoital oral contraceptive, setting forth the text of patient labeling for that use, and providing for and inviting abbreviated new drug applications. Sixty days were provided for comment on the proposal.

An amendment to the proposed restructured paragraph (a) was published in the FEDERAL REGISTER of April 19, 1974 (39 FR 13972), upon which, since it is still under consideration, action will be taken at a later date.

In response to the September 1973 proposal, comments were received from 21 persons including several from consumer organizations, one from a religious organization, one from a municipality, one from a private physician, one from an individual employed by a pharmaceutical concern, and several from private individuals.

One abbreviated new drug application has been received.

Three respondents endorsed the proposal. Several endorsed the concept of requiring patient labeling, but were critical of its proposed content. The remainder were generally opposed to approval of DES for oral contraception. The comments, organized into categories, and the Commissioner's response with respect to each, are as follows:

1. Some comments asserted that DES is a dangerous drug due to its carcinogenic potential both to the fetus and to the mother, and should not be allowed on the market. One comment urged that the leaflet state more honestly the risk to the offspring when exposed in utero to DES. It was also requested that the patient leaflet indicate that there is some risk of cancer to the patient herself from taking DES.

In considering the use of DES as a postcoital oral contraceptive, the Commissioner has carefully reviewed all available data and also consulted with the Obstetrics and Gynecology Advisory Committee for the Food and Drug Administration on the issues of both safety and effectiveness.

a. Fetal risks: It has been reported by Herbst et al. in *The New England Journal of Medicine* of April 22, 1971 (284: 878–881) that DES, if taken, usually for a prolonged period, by a woman who is pregnant, increases the risk of carcinoma of the vagina or cervix in the female offspring. It has been estimated that less than one percent of the offspring of women who have received DES treatment during pregnancy have developed cancer. The directions for use proposed for DES state that pregnancy should be ruled out prior to use of the drug. Obviously, if there is no pre-existing or ensuing pregnancy, issues involving a fetus are moot. Where it is later discovered that there is a pre-existing or ensuing pregnancy, however, the patient package insert advises that the patient consult with her physician regarding the continuation of the pregnancy. The physician's labeling also fully discusses this issue.

In order to emphasize this risk, the former fourth sentence in the third paragraph of the patient package insert, set forth in the proposal published in the FEDERAL REGISTER of September 26, 1973, has been revised to delete the word "some" preceding "evidence" and to change the word "may" to "will" in the phrase "the child may have an increased risk of developing cancer of the vagina or cervix later in life." This discussion has also been highlighted by setting it out separately as a new fourth paragraph.

Although it was stated in paragraph (b)(2) of the proposed regulation that teratogenic and other adverse effects on the fetus with the very early administration recommended are not well understood, this was not mentioned in the proposed patient package insert. The Commissioner concludes that it should be mentioned. The patient package insert accordingly contains the following statement as the third sentence of the new fourth paragraph: "Also, it is not definitely known whether this drug may cause other abnormalities in the fetus." The statement is also included in the labeling for the physician.

b. Adult risks: In *The New England Journal of Medicine* of September 28, 1972 (287: 628–631) Cutler et al. reported the occurrence of endometrial carcinoma after stilbestrol therapy in patients with gonadal dysgenesis who were treated with the drug for long periods of time, i.e., 5 years or more. For many years there has been concern that estrogens, both exogenous and endogenous, may have an etiological role in the development of cancer of the genital tract or breast. The observation felt to support this is that certain functioning ovarian tumors, such as granulosa cell and theca cell types which secrete large amounts of estrogen, are associated with an increased frequency of carcinoma of the endometrium. The paper by Cutler et al. may also be considered to support this possibility for certain unusual circumstances. Cutler's cases all had chromosomal abnormalities (only one X chromosome instead of the normal two) and the authors themselves observe that a genetic predisposition of such patients to this type of cancer, enhancing the effect of prolonged estrogen therapy, cannot be excluded. They further point out that abnormal chromosomal constitutions are known to be associated with an increased incidence of specific types of malignant tumors. The Commissioner concludes that the study of Cutler et al. is not applicable to a 5-day course of DES in normal women because the Cutler study involved the cyclic administration of DES for many years to women with chromosomal abnormalities. Therefore, in spite of the Cutler study, there continues to be no relevant evidence at the present time that a short course of DES in normal women, as would be used in postcoital contraception, would expose a woman to an increased risk of cancer. At the same time, it cannot be said that such a risk definitely does not exist.

The Commissioner recognizes that the patient package insert, as originally proposed, did not deal with the carcinogenicity of DES in animals and the possible relevance of these data to human use. In the regulation previously promulgated concerning oral contraceptives, § 310.501 (a)(6)(xi) requires that patient information include a statement regarding production of cancer in certain animals, and provides that such statement may be coupled with a statement that there is no proof of such effect in human beings.

The Commissioner concludes that such a requirement is equally applicable for the patient information to be supplied with DES as a postcoital oral contraceptive. Accordingly, the last sentence in the third paragraph of the proposed patient package insert has been deleted and is replaced by a new fifth paragraph, which cites the tests conducted in animals resulting in increased frequency of cancer, and warns that high dosages of estrogen are recommended for emergencies only, and not for repeated use.

c. Effectiveness: The Commissioner concludes that data from clinical investigations provide substantial evidence that DES is effective in preventing conception; however, its effectiveness depends upon close adherence to the dosage regimen of 25 milligrams twice a day for 5 consecutive days, with initiation of administration preferably within 24 hours and not later than 72 hours after coitus. On reconsideration, the Commissioner believes the words "highly effective," which appeared in the proposed patient package insert, may be misconstrued by some readers to imply a greater degree of effectiveness than other forms

of contraception or to imply that this treatment is always successful. To minimize the possibility of such misconception, the words "highly effective" in the first sentence of the third paragraph of the proposed patient package insert and in the last sentence of § 310.501(b)(1) have been changed to "usually effective."

The following studies are regarded as providing substantial evidence of effectiveness:

(1) Morris, J. M. and G. van Wagenen, "Postcoital Oral Contraception," Proc. 8th Int. Conf. International Planned Parenthood Federation, Santiago, 1967, p. 256.

(2) Kuchera, L. K., "Postcoital Contraception with Diethylstilbestrol," *Journal of the American Medical Association* 4:562, 1971.

The following studies and review paper provide supportive evidence of effectiveness:

(1) Morris, J. M. and G. van Wagenen, "Compounds Interfering with Ovum Implantation and Development," *American Journal of Obstetrics and Gynecology* 96:804, 1966.

(2) Haspel, A. A., "The Effect of Large Doses of Oestrogens Postcoitum in 2000 Women." Unpublished paper (available from the Food and Drug Administration).

(3) Morris, J. M. and G. van Wagenen, "Interception: The Use of Postovulatory Estrogens to Prevent Implantation," *American Journal of Obstetrics and Gynecology* 115: 101, 1973.

(4) Blye, R. P., "The Use of Estrogens as Postcoital Contraceptive Agents," *American Journal of Obstetrics and Gynecology* 115: 1044, 1973. Presented at the 26th meeting of the Obstetrics and Gynecology Advisory Committee to the Bureau of Drugs, Food and Drug Administration, January 26, 1973. This paper reviewed the studies currently available in support of the efficacy of DES as well as other estrogens (ethinyl estradiol, conjugated equine estrogens, dienestrol, estradiol cyclopentylpropionate). This paper supports the finding that estrogens are biologically effective as contraceptive agents and that there is need to determine the appropriate safe and effective dose with respect to each estrogen.

2. Several comments contended that DES is an abortifacient and not a contraceptive.

The exact mechanism of action through which DES prevents pregnancy when used postcoitally is presently unknown. There have been several theories advanced as to the mechanism, including interference with nidation through effects on the endometrium (the most likely), accelerated tubal transport of ovum, closure of the uterotubal junction, and luteolytic activity. The definition of an abortifacient is a matter of controversy. On the one hand, it may be defined as a drug or device which is capable of destroying an implanted ovum. Under this definition, DES cannot be an abortifacient because it cannot do this. Alternatively, an abortifacient could be defined as a drug or device which can prevent implantation of a fertilized ovum. Intrauterine devices and certain oral contraceptives are considered by experts to act, at least in part, by preventing implantation. These devices and drugs are generally classified as contraceptives rather than abortifacients. There is no scientific basis for distinguishing DES from such oral drugs or intrauterine devices on the basis of mechanism of action.

Since classification of DES as an abortifacient would be arbitrary unless many other devices and drugs were similarly classified, the Commissioner concludes it is proper to call DES a contraceptive.

3. A number of persons expressed considerable concern regarding what they construed as a "recommendation" that abortion be performed in the event that the method fails.

The patient package insert advises the patient to consult with her physician regarding continuation of the pregnancy if there is pre-existing pregnancy or if pregnancy ensues. The final decision as to the course of action to be taken rests with the patient and her physician. Thus, there is no "recommendation" that an abortion be performed.

4. One comment requested that the patient leaflet make it clear that the drug is for emergency use only, and define exactly what emergency use is.

The Commissioner agrees that the patient package insert should make it quite clear that this use is an emergency measure and that it is not to be used as a routine or frequent method of contraception. Therefore, in order to emphasize this, the first sentence in the first paragraph of the patient package insert has been changed by revising the phrase "emergency measure to prevent pregnancy" to read "measure to prevent pregnancy in an emergency, for example, after a rape." In addition, the second paragraph of the patient package insert has been revised to state: "You should use this drug only under the direction of your physician. This treatment is for emergencies only and should not be used repeatedly. If you find it necessary to use this treatment more than once, you should consult with your physician to obtain an adequate method of routine contraception." Finally, the point is again emphasized in the new fifth paragraph of the patient package insert.

The Commissioner believes that these additions to the patient package insert provide sufficient emphasis that DES is intended for emergency use only, but that a definition of what constitutes an emergency is unnecessary and should properly be left to the patient and her physician.

5. A comment stated that women should be fully informed concerning possible side effects. Another suggested that all possible contraindications to the drug be included in the patient package insert.

The Commissioner agrees with these comments. All contraindications to the use of the drug are listed in the patient package insert. The patient package insert does list the most common as well as the most serious adverse effects which may be encountered with the use of an estrogenic preparation such as DES. Additionally, the patient package insert does list special health problems that should be brought to the attention of the physician. Each and every side effect associated with the use of DES is not listed in the patient package insert because, although they apply to estrogens as a class, they have not been associated with the use of DES as a postcoital contraceptive to an appreciable extent. All side effects are listed in the package insert intended for the physician and such information should be readily available to the patient from her physician if she requests it. Furthermore, the physician's package insert states in the "Important Notes" section that "patients should be informed of . . . all other existing information relative to known and potential side effects prior to use of DES for this indication."

In order to discourage use for postcoital contraception of dosage strengths of DES other than the 25 mg. tablets which are accompanied by the patient package insert, the physician's package insert for such dosage strengths will be required to include the following in block letters before the description:

THIS DRUG PRODUCT SHOULD NOT BE USED AS A POSTCOITAL CONTRACEPTIVE

A FEDERAL REGISTER notice will be published in the near future setting forth this requirement.

6. It was requested that users of DES be strongly cautioned to contact a physician if they are pregnant, because of the association between DES and carcinoma of the vagina in female offspring.

The Commissioner agrees and notes that the patient package insert does recommend that the patient consult her physician regarding continuation of pregnancy in the event the drug is not successful.

7. One comment requested that a medical history of the patient be taken, including any history of cancer in the family.

Good medical practice dictates that an appropriate medical history be taken prior to initiation of therapy with any drug. Thus, the Commissioner concludes that such a statement is unnecessary and inappropriate for inclusion in any drug labeling.

8. A comment urged that patient followup be made to assure that the patient did not become pregnant, to discover possible adverse side effects, and to determine pregnancy rates associated with this use of DES.

In order to assure patient followup in the event that pregnancy occurs, the Commissioner has concluded that the sixth sentence in the original third paragraph of the proposed patient package insert should be deleted and replaced by a new sentence inserted at the end of the new fourth paragraph, to read as follows: "If you have not had a normal menstrual period within 4 weeks after taking the last tablet, you should contact your physician to determine if you are pregnant, and if you are, consult with him regarding continuation of the pregnancy."

With respect to adverse effects, the proposed labeling informs the patient that if any of the serious adverse effects mentioned in the labeling are noted, these should be reported to her physician.

With respect to collecting data on adverse effects and pregnancy rates associated with this treatment, it is highly unlikely that meaningful and valid results could be obtained unless such followup visits were done as part of a controlled study.

9. Two comments contended that provisions for informed patient consent are inadequate and that written consent should be required in some cases.

The Commissioner concludes that the patient who has consulted her physician, discussed her problem with him, and read her patient package insert, will ordinarily be adequately informed. The physician may consult with a parent or guardian if he finds it appropriate or necessary. If experience should prove that the present requirements do not ensure that patients are adequately informed, the Commissioner will consider other measures.

10. One comment recommended that every possible attempt be made to ensure that a patient is never prescribed DES for this particular indication more than once.

Both the patient package insert and the physician's package insert indicate that DES is not to be used routinely or frequently as a method of contraception, and draw attention to the lack of evidence of safety in repeated use. This point is now emphasized in both the second and fifth paragraphs of the revised patient package insert. The Commissioner believes that this labeling adequately discloses current knowledge to both physician and patient and that further measures to limit usage are not warranted at this time.

11. One comment objected to the proposal and requested that the reasons for his objections be explored in public hearings.

The regulation proposed is not the type of regulation on which the Food and Drug Administration is required to hold a public hearing, although the Commissioner may exercise his discretion in that regard. The topic of DES as a postcoital contraceptive was considered during a public hearing at the open session of the Obstetrics and Gynecology Advisory Committee on January 26, 1973. Anyone wishing to present his views on this subject was invited to do so and several people availed themselves of this opportunity either through personal appearance or through correspondence. Their views were carefully considered by the members of the Advisory Committee and by the Food and Drug Administration in reaching their final decision relative to DES as a postcoital contraceptive. The Commissioner has carefully considered the data and information available, finds that the proposed approval of DES as a postcoital contraceptive is justified by the facts, and concludes that a further public hearing at this time on this matter would serve no useful purpose.

The Commissioner, having considered the comments received, finds no basis for altering his finding that DES is safe and effective as a postcoital contraceptive for emergency use when used under the conditions proposed, and concludes that, except for the revisions in the patient package insert and the regulation noted above, the regulation shall be promulgated as proposed.

Shipment in interstate commerce of diethylstilbestrol for use as a postcoital contraceptive is unlawful unless such use is provided for in an approved new drug application as described in the regulation below.

The references cited in this preamble, and other related background material have been assembled and are on display in the office of the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20852. The following is a list of the material on display:

(1) Proposed DES regulation. FEDERAL REGISTER, September 26, 1973.

(2) Notice that DES is contraindicated in pregnancy FEDERAL REGISTER, November 10, 1971.

(3) "Postcoital Diethylstilbestrol," FDA Drug Bulletin, May 1973.

(4) "Diethylstilbestrol Contraindicated in Pregnancy," FDA Drug Bulletin, November 1971.

(5) Obstetrics and Gynecology Advisory Committee: Minutes of December 1971 meeting. Material not relevant to DES has been deleted.

(6) Obstetrics and Gynecology Advisory Committee: Minutes of March 1972 meeting. Material not relevant to DES has been deleted.

(7) Obstetrics and Gynecology Advisory Committee: Minutes of January 1973 meeting (both open and closed sessions).

(8) Results of NIH/FDA Workshop on Pregnancy Prevention by Estrogens, held February 14, 1972.

(9) Kuchera, L. K., M.D., "Postcoital Contraception with Diethylstilbestrol," *Journal of the American Medical Association 4:* 562–563, 1971.

(10) Haspels, A. A., M.D., "The Effect of Large Doses of Oestrogens Post-Coitum in 2000 Women." Unpublished paper.

(11) Connell, E. B., M.D., "New York State Survey on 'Morning After' Estrogen Contraceptive Therapy," report presented at NIH Workshop on Aversion of Pregnancy by Estrogens, held February 14, 1972.

(12) Herbst, A. L., et al., "Adenocarcinoma of the Vagina," *New England Journal of Medicine* 284:878–881, 1971.

(13) Cutler, B. S., et al., "Endometrial Carcinoma after Stilbestrol Therapy in Gonadal Dysgenesis," *New England Journal of Medicine* 287:628–631, 1972.

(14) Morris, J. M., et al., "Compounds Interfering with Ovum Implantation and Development," *American Journal of Obstetrics and Gynecology* 96:804, 1966.

(15) Morris, J. M., et al., "Post-Coital Oral Contraception." Proc. 8th Int. Conf. International Planned Parenthood Federation, Santiago, 1967, p. 256.

(16) Blye, R. P., "The Use of Estrogens as Postcoital Contraceptive Agents," *American Journal of Obstetrics and Gynecology* 7:1044, 1973.

(17) Morris, J. M. and G. van Wagenen, "Interception: The Use of Postovulatory Estrogens to Prevent Implantation," *American Journal of Obstetrics and Gynecology* 115:101, 1973.

(18) Morris, J. M., "Mechanisms Involved in Progesterone Contraception and Estrogen Interception," *American Journal of Obstetrics and Gynecology* September 15, 1973.

Accordingly, the Commissioner concludes that § 310.501 should be amended by revising the section heading; redesignating paragraph (a) as paragraph (a)(1) and adding a new heading for paragraph (a); redesignating paragraph (b) as paragraph (a)(2); redesignating the remainder of the existing paragraphs as subparagraphs of paragraph (a) with no change in the existing text; and by adding a new paragraph (b).

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502(a) and (f), 505, 701(a), 52 Stat. 1050–1053, 1055, as amended; 21 U.S.C. 352(a) and (f), 355, 371(a)) and under authority delegated to him (21 CFR 2.120), Part 310 is amended by revising § 310.501 to read as follows:

§ 310.501 Preparations for contraception; labeling directed to the patient.

(a) *Oral contraceptives.* (1) The Food and Drug Administration is charged with assuring both physicians and patients that drugs are safe and effective for their intended uses. The full disclosure of information to physicians concerning such things as the effectiveness, contraindications, warnings, precautions and adverse reactions is an important element in the discharge of this responsibility. In view of this, the Administration has reviewed the oral contraceptive products, taking into account the following factors: The products contain potent steroid hormones which affect many organ systems; they are used for long periods of time by large numbers of women who, for the most part, are healthy and take them as a matter of choice for prophylaxis against pregnancy, in full knowledge of other means of contraception; and there is no present assurance that persons for whom the drugs are prescibed or dispensed are uniformly being provided the necessary information for safe and effective use of the drugs.

(2) In view of the foregoing, it is deemed in the public interest to present to users of the oral contraceptives a brief notice of the nature of the drugs, the fact that continued medical supervision is needed for safe and effective use, that the drugs may cause side effects and are contraindicated in some cases, that the most important complication is abnormal blood clotting which can have a fatal outcome, that the physician recognizes an obligation to discuss the potential hazards of taking the drugs with the patient, that he has available for the patient written material discussing the effectiveness and the hazards of the drugs, and that users of the oral contraceptives should notify their physicians if they notice any unusual physical disturbance or discomfort.

(3) The Commissioner agrees that the physician is the proper person for providing use information to his patients,

and these regulations will provide him a balanced discussion of the effectiveness and the risks attendant upon the use of oral contraceptives for his use in discussing the drugs with his patients.

(4) The oral contraceptives are restricted to prescription sale, and their labeling is required to bear information under which practitioners licensed to administer the drugs can use them safely and for the purpose for which they are intended. In addition, in the case of oral contraceptive drugs, the Commissioner conclude that it is necessary in the best interests of users that the following printed information for patients be included in or with the package dispensed to the patient:

(Patient Package Information)

ORAL CONTRACEPTIVES

(Birth Control Pills)

Do Not Take This Drug Without Your Doctor's Continued Supervision

The oral contraceptives are powerful and effective drugs which can cause side effects in some users and should not be used at all by some women. The most serious known side effect is abnormal blood clotting which can be fatal.

Safe use of this drug requires a careful discussion with your doctor. To assist him in providing you with the necessary information, _____ has prepared a booklet (or other form) written in a style understandable to you as the drug user. This provides information on the effectiveness and known hazards of the drug including warnings, side effects and who should not use it. Your doctor will give you this booklet (or other form) if you ask for it and he can answer any questions you may have about the use of this drug.

(Firm name)

Notify your doctor if you notice any unusual physical disturbance or discomfort.

(5) Providing the patient package information to users may be accomplished by including it in each package of the type intended for the user as follows:

(i) If such package includes additional printed materials for the patient (e.g., dosage schedules), the text of the information in paragraph (a)(4) of this section shall be an integral part of the printed material and be in boldface type set out in a box, preceding all other printed text.

(ii) If such package does not include other printed material for the patient, the text of the information in paragraph (a)(1) of this section shall be provided as a printed leaflet in boldface type.

(iii) Include in each bulk package intended for multiple dispensing a sufficient number of the patient package information leaflets, with instructions to the pharmacist to include one with each prescription dispensed.

(6) Written, printed, or graphic materials on the use of a drug that are disseminated by or on behalf of the manufacturer, packager, or distributor and are intended to be made available to the patient, are regarded as labeling. The commissioner also concludes that it is necessary that information in lay language, concerning effectiveness, contraindications, warnings, precautions, and adverse reactions be incorporated prominently in the beginning of any such materials, and that such labeling must be made available to physicians for all patients who may request it. Such labeling shall be substantially as follows, based on the approved package insert for prescribers of the oral contraceptives, and shall include the following points:

(i) A statement that the drug should be taken only under continued supervision of a physician.

(ii) A statement regarding the effectiveness of the product.

(iii) A warning regarding the serious side effects with special attention to thromboembolic disorders and stating the estimated morbidity and mortality in users vs. nonusers. Other serious side effects to be mentioned include mental depression, edema, rash, and jaundice. The possibility of infertility following discontinuation of the drug should be mentioned.

(iv) A statement of contraindications.

(v) A statement of the need for special supervision of some patients including those with heart or kidney disease, asthma, high blood pressure, diabetes, epilepsy, fibroids of the uterus, migraine, mental depression or history thereof.

(vi) A statement of the most frequently encountered side effects such as spotting, breast changes, weight changes, skin changes, and nausea and vomiting.

(vii) A statement of the side effects frequently reported in association with the use of oral contraceptives, but not proved to be directly related, such as nervousness, dizziness, changes in appetite, loss of scalp hair, increase in body hair, and increased or decreased libido.

(viii) A statement regarding metabolic effects such as on blood sugar and cholesterol setting forth our current lack of knowledge regarding the long term significance of these effects.

(ix) Instructions in the event of missed menstrual periods.

(x) A statement cautioning the patient to consult her physician before resuming the use of the drug after childbirth, especially if she intends to breastfeed the baby, pointing out that the hormones in the drug are known to appear in the milk and may decrease the flow.

(xi) A statement regarding production of cancer in certain animals. This may be coupled with a statement that there is no proof of such effect in human beings.

(xii) A reminder to the patient to report promptly to her physician any unusual change in her general physical condition and to have regular examinations.

Optionally, the booklet may also contain factual information on family planning, the usefulness and hazards of other available methods of contraception, and the hazards of pregnancy. This material shall be neither false nor misleading in any particular and shall follow the material presented above.

(7) The marketing of oral contraceptives may be continued if all the following conditions are met on or before May 6, 1975, the date of publication of this section in the FEDERAL REGISTER.

(i) The labeling of such preparations shipped within the jurisdiction of the Act is in accord with paragraph (a)(4), (5), and (6) of this section.

(ii) The holder of an approved new-drug application for such preparation submits a supplement to his new drug application under the provisions of § 314.8(d) of this chapter to provide for labeling as described in paragraph (a)(4), (5) and (6) of this section. Such labeling may be put into use without advance approval of the Food and Drug Administration.

(iii) Existing stocks may be shipped without the package insert for a period of 90 days, provided the labeling booklet is prepared and disseminated as promptly as possible.

(b) *Oral postcoital contraceptives.* (1) Diethylstilbestrol orally for postcoital contraception. Studies conducted with this drug have shown its effectiveness in contraception when administered under restricted conditions. The Commissioner, having considered comments by members of the Food and Drug Administration's Obstetrics and Gynecology Advisory Committee, concludes that the drug is safe and effective as an emergency treatment only, and not as a routine method of birth control. Repeated courses of therapy are to be avoided. The effectiveness of diethylstilbestrol in preventing pregnancy depends upon the time lapse after coitus and administration of the drug. The recommended dosage is one 25 milligram tablet twice a day, for 5 consecutive days beginning, preferably, within 24 hours and not later than 72 hours after exposure. When this dosage is given within the specified time interval, the drug is usually effective in preventing conception. Its use, however, will not terminate pregnancy.

(2) There is at present no positive evidence that the restricted use of diethylstilbestrol for postcoital contraception carries a significant carcinogenic risk either to the mother or the fetus. However, because existing data support the possibility of delayed appearance of carcinoma in females whose mothers have been given diethylstilbestrol later in pregnancy, and because teratogenic and other adverse effects on the fetus with the very early administration recommended are not well understood, failure of postcoital treatment with the drug deserves serious consideration of voluntary termination of pregnancy. For these reasons, as well as possible adverse effects in the patient, the drug should not be used as a routine method of birth control. A pregnancy test should be performed prior to use of the drug as a postcoital contraceptive. If the test is positive, the drug should not be used.

(3) Because of the nature of the conditions surrounding this use of diethylstilbestrol, the Commissioner concludes that it is in the best interests of the patient that, in addition to receiving specific instructions from her physician, she also receive with her package of the drug

a printed leaflet describing how to use the drug, limitations on its use, its potential for serious effects on the fetus in the event she is pregnant, and possible adverse effects, contraindications and precautions.

(4) Diethylstilbestrol for use as a postcoital contraceptive shall be packaged in containers of 10 tablets, each tablet to contain 25 milligrams diethylstilbestrol. Each drug package of 10 tablets shall contain, in addition to information under which the practitioner licensed to administer the drug can use it safely and for the purpose for which it is intended, a brief leaflet for the user to read as follows:

(Patient package information)

Your doctor has prescribed these tablets which contain estrogen (female hormone) as a measure to prevent pregnancy in an emergency, for example, after a rape. To be effective the treatment must be started within 3 days of sexual intercourse and preferably within 1 day. Also, you must take the full course of tablets (1 twice a day for 5 days) even if some nausea and vomiting occurs. These symptoms are common in patients receiving this medicine.

You should use this drug only under the direction of your physician. This treatment is for emergencies only and should not be used repeatedly. If you find it necessary to use this treatment more than once, you should consult with your physician to obtain an adequate method of routine contraception.

This treatment is usually effective in preventing pregnancy if used as described above. However, this drug will not cause an abortion if you are already pregnant. Before prescribing this drug, your physician will determine whether or not you may be pregnant.

An important reason for not taking the drug if you are already pregnant is that such usage exposes the fetus to an unnecessary hazard. There is evidence that, if the growing fetus is a female and the mother is given this drug during pregnancy, the child will have an increased risk of developing cancer of the vagina or cervix later in life. Also, it is not definitely known whether this drug may cause other abnormalities in the fetus. If you have not had a normal menstrual period within 4 weeks after taking the last tablet, you should contact your physician to determine if you are pregnant; and if you are, consult with him regarding continuation of the pregnancy.

In tests conducted in animals, estrogens given for long periods have increased the frequency of cancer in certain species. While there is no evidence from currently available studies in women to indicate that you will have an increased risk of developing cancer later in life if you use this treatment, there is no way to be certain that such evidence will not appear in the future. Therefore, it is sensible and prudent to avoid the high dose of estrogen used in this treatment unless absolutely necessary. That is why this method of contraception is recommended for emergency use only and should not be used repeatedly.

These tablets which contain estrogen may cause certain side effects, most of which are not serious. The most common side effects are nausea, vomiting, breast tenderness and swelling. The most serious side effect of estrogens, which is rare but can at times be fatal, is abnormal blood clotting, the symptoms of which may be severe leg or chest pain, coughing up of blood, difficulty in breathing, sudden severe headaches, dizziness or fainting, disturbances in vision or speech or weakness or numbness of an arm or leg. If any of these occur, you should stop taking the tablets and notify your doctor as soon as possible.

Women who have or have had blood clotting disorders, serious liver conditions, cancer of the breast or womb, or undiagnosed vaginal bleeding in the past should not take these tablets. Furthermore, you should inform your physician if you have or have had a special health problem, such as migraine, mental depression, fibroids of the uterus, heart or kidney disease, asthma, high blood pressure, diabetes or epilepsy. He may wish to make sure that it is suitable for you to take these tablets.

(5) Diethylstilbestrol for use as a postcoital contraceptive may be marketed only on the basis of an approved new drug application containing information required by § 314.1(f) of this chapter, except that full information described under items 7 and 8 (composition and methods, facilities, and controls) of the new drug application Form FD-356H (§ 134.1(c) of this chapter) is required. Guidelines for labeling directed to the physician are available from the Food and Drug Administration, Bureau of Drugs, Division of Metabolic and Endocrine Drug Products (HFD-130), 5600 Fishers Lane, Rockville, MD 20852.

Effective date: This order shall be effective on March 7, 1975.

(Secs. 502 (a) and (f), 505, 701(a), 52 Stat. 1050–1053, 1055, as amended; 21 U.S.C. 352 (a) and (f), 505, 701(a).)

Dated: January 30, 1975.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

[FR Doc.75-3201 Filed 2-4-75;8:45 am]

PART 442—CEPHA ANTIBIOTIC DRUGS

Cephalothin Sodium for Injection

The Commissioner of Food and Drugs has evaluated data submitted in accordance with regulations promulgated under section 507 of the Federal Food, Drug, and Cosmetic Act, regarding approval of the antibiotic drug cephalothin sodium for injection.

The Commissioner concludes that data supplied by the manufacturer about this antibiotic drug are adequate to establish its safety and efficacy when used as directed in the labeling, and that the regulations should be amended to provide for its certification, effective immediately.

Therefore, under provisions of the Federal Food, Drug, and Cosmetic Act (sec. 507, 59 Stat. 463, as amended; 21 U.S.C. 357) and under authority delegated to the Commissioner (21 CFR 2.120), Part 442 in Subchapter D of Chapter I of Title 21, of the Code of Federal Regulations, is amended in Subpart C by adding the following new section to provide for certification of the antibiotic drug product cephalothin sodium for injection:

§ 442.225c Cephalothin sodium for injection.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Cephalothin sodium for injection is a dry mixture of cephalothin sodium with one or more suitable and harmless buffer substances. Its potency is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of cephalothin that it is represented to contain. It is sterile. It is nonpyrogenic. It passes the safety test. Its loss on drying is not more than 1.5 percent. When reconstituted as directed in the labeling, its pH is not less than 6.0 and not more than 8.5. The cephalothin sodium used conforms to the standards prescribed in § 442.25a(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The cephalothin sodium used in making the batch for potency, loss on drying, pH, specific rotation, identity, and crystallinity.

(*b*) The batch for potency, sterility, pyrogens, safety, loss on drying, and pH.

(ii) Samples required:

(*a*) The cephalothin sodium used in making the batch: 10 packages, each containing approximately 500 milligrams.

(*b*) The batch:

(*1*) For all tests except sterility: A minimum of 10 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency.* Use either of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(i) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Reconstitute the sample as directed in the labeling. Using a suitable hypodermic needle and syringe, remove an accurately measured representative portion from each container and dilute with sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Further dilute an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 microgram of cephalothin per milliliter (estimated).

(ii) *Hydroxylamine colorimetric assay.* Proceed as directed in § 436.205 of this chapter, preparing the sample for assay as follows: Reconstitute the sample as directed in the labeling. Using a suitable hypodermic needle and syringe, remove an accurately measured representative portion from each container and dilute with distilled water to give a stock solution of convenient concentration. Further dilute with distilled water to the prescribed concentration.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.